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TITLE: Gulf War Illness Inflammation Reduction Trial

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14. ABSTRACT

The objective of this clinical trial is to find an evidence-based treatment for Gulf War Illness (GWI). Elevated biomarkers of inflammation were observed in our pilot observational study of GWI. Thus, chronic inflammation appears to be part of the underlying pathophysiology of GWI. Reducing GWI-associated inflammation may alleviate some symptom of the disorder and improve the health-related quality of life of veterans with GWI. This is a randomized, two-group, double-blind, placebo-controlled clinical trial of delayed-release prednisone versus matching placebo. A total of 100 veterans with GWI will be enrolled in the trial. Prednisone was chosen as the study drug because of its well-established pleiotropic anti-inflammatory properties. The specific aims of the study are to measure the effects of the treatment on the following: 1) physical and mental functioning 2) pain, fatigue, and cognitive dysfunction 3) biomarkers of inflammation. All regulatory approvals for this clinical trial have been received. Recruitment and enrollment have begun. A successful trial with improved clinical outcomes and reduced proinflammatory biomarkers would be direct evidence of the role that chronic inflammation plays in the underlying pathophysiology of GWI. Thus, a new paradigm for the diagnosis and treatment of GWI would be established. The potential impact of this new paradigm on the health and well-being of veterans with GWI is significant.

15. SUBJECT TERMS

Gulf War Illness, Chronic Inflammation, Delayed-Release Prednisone

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Introduction

Today approximately one-third of the 696,841 U.S. military personnel who served in the 1990-1991 Gulf War are suffering from an unexplained chronic multi-symptom illness that is commonly referred to as Gulf War Illness (GWI) (1, 2). The absence of information regarding the underlying pathophysiology of GWI has hindered efforts to develop effective treatments. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans with and without multiple symptoms of pain, fatigue, and cognitive dysfunction. The goal of the pilot study was to identify a potential therapeutic target for the treatment of GWI. Examination to the peripheral blood revealed the biomarker signature of innate immune system activation in veterans with GWI. Thus, chronic inflammation was identified as a potential therapeutic target.

Key Words

Gulf War Illness, Chronic Inflammation, Delayed-Release Prednisone, Evidence-Based Treatment, Double-Blind Placebo-Controlled Clinical Trial, Pain, Fatigue, Cognitive Dysfunction

Accomplishments

1st Quarter

- The Cooperative Research and Development Agreement (CRADA) between the Minneapolis VA Health Care System (MVAHCS) and Horizon Pharma has been signed. Horizon Phama will supply both the study drug (delayed-release prednisone) and matching placebo at no cost.
- The IRB application for the Gulf War Illness Inflammation Reduction Trial was submitted to the MVAHCS IRB.
- The IRB application was approved with stipulations.
- The revised IRB application has been resubmitted to the MVAHCS IRB.
- The essential study staff ,i.e. the Study Coordinators, were hired.

2nd Quarter

- The Authorization to Conduct Research (ACR) for the Gulf War Illness Inflammation Reduction Trial (GW 130025) was issued by the MVAHCS Research and Development Committee (RDC).
- All the necessary documents were submitted to the United States Army Research and Materiel Command Human Research Protection Office (HRPO) for review and approval.

3d Quarter

- HRPO reviewed the documents and stipulated changes.
- The changes were made to the documents and the amendments were submitted to and approved by the Minneapolis VAMC IRB.

- Following local IRB approval the documents were resubmitted to HRPO. They review and approved the application.
- The clinical trial has received all the regulatory approvals.

4th Quarter

- The Gulf War Illness Inflammation Reduction Trial was posted on ClinicalTrials.gov.
- In accord with the Cooperative Research and Development Agreement (CRADA) between the Minneapolis VA Health Care System (MVAHCS) and Horizon Pharma the study drug (Rayos, delayed-release prednisone) and matching placebo has been shipped to the Minneapolis VAMC Research Pharmacist.
- The first batch of recruitment letters were mailed on 06-07-2015. The rate of recruiting is ~25 letters per week.
- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) have begun.

Progress as of 30-09-2015:

Recruitment letters sent …….205
Recruits who responded to the letter…….23
Recruits who passed the initial GWI telephone screen……11
Screened recruits who agreed to participate in the trial……11
Potential subjects who have been consented and passed screening visit safety checks……7
Enrolled subjects who have received study drug or placebo…….7
Potential subjects who have been scheduled for screening visit.……4

Rate of recruitment anticipated in grant proposal……..0.62 subjects per week
Actual rate of recruitment……0.93 subject per week

Impact

In 1995 the Department of Veterans Affairs (VA) initiated a retrospective cohort survey of 15,000 deployed and 15,000 non-deployed Gulf War era veterans (3). A second study reexamined the health status of the veterans who participated in the 1995 baseline survey (4). This work identified the prevalence of multi-symptom illnesses as the most significant difference between the deployed and non-deployed veterans (36.5% vs. 11.7%, adjusted risk ratio = 3.05). Thus, GWI became the signature health-related outcome of the Gulf War.

The underlying pathophysiology of GWI is not understood. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans who very GWI- with blood

from veterans who were GWI+. The GWI status was determined by the assessment of multiple symptoms of pain, fatigue, and cognitive dysfunction using the CDC 10 survey instrument. The objective of the study was to determine if there are quantifiable differences in blood that could be used to identify potential therapeutic targets for the treatment of GWI. The blood analyses included a complete blood count with differential, plasma proteomics, platelet function studies, and the measurement of multiple coagulation parameters.

The pilot study results provide strong evidence of chronic inflammation in veterans with GWI. This entirely new and provocative line of evidence presents an exciting opportunity to test an intervention that has the potential to both reduce symptoms and further define the pathophysiology of GWI.

The goal of this proof-of-principal trial is to determine if reducing inflammation is an effective treatment for GWI. A successful trial with improved clinical outcomes and reduced biomarkers of inflammation would establish a new paradigm for the diagnosis and treatment of GWI. The testing of other therapeutic interventions designed to reduce inflammation and minimize toxicity could produce additional improvements in GWI treatment beyond those achieved in this trial. The immediate and long-term positive consequences for the health and well-being of veterans with GWI would be significant.

Changes/Problems

None

Products

None

Participants & Other Collaborating Organizations

Name:	Ronald R. Bach, PhD
Project Role:	P.I.
Nearest person month worked:	3
Contribution to Project:	Dr. Bach has overseen the efforts of other study personnel with respect to the regulatory approval process as well as screening, enrollment, and conduct of the study.

Name:	Rebecca Rudquist, BSN
Project Role:	Study Coordinator
Nearest person month worked:	10
Contribution to Project:	Ms. Rudquist has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Name:	Susan Johnson, LPN
Project Role:	Study Coordinator
Nearest person month worked:	5
Contribution to Project:	Ms. Johnson has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Special Reporting Requirements

None

Appendices

None

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